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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/966,803	09/27/2001	Jay Short	DIVER1130-8	3294

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EXAMINER	
RAMIREZ, DELIA M	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 05/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/966,803	SHORT ET AL.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42-55 and 93-106* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42-55 and 93-106* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/17/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Claims 42-55 and 93-106 are pending.

Applicant's amendment of claims 42-55, cancellation of claims 1-41 and 56-92, addition of claims 93-106, submission of a declaration under 37 CFR 1.132 by Dr. Jay Short, and amendments to the specification, in a communication filed on 2/17/2004 are acknowledged.

As requested by Applicants on page 14 of the response filed on 2/17/2004, the Examiner attempted to contact Applicant's representative on 4/28/2004 to discuss the issues raised in the first Office Action.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Information Disclosure Statement

1. The information disclosure statement (IDS) submitted on 2/17/2004 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Specification

2. The specification remains objected to as it recites trademarks which have not been capitalized. While Applicants assert in the Remarks section of the response filed on 2/17/2004 that the specification has been amended to capitalized trademark products, it is noted that no amendment capitalizing trademarks has been found. See, for example page 51, paragraph 165. Appropriate correction is required.

Drawings

3. The drawings submitted on 2/17/2004 are approved by the Examiner.

Claim Objections

4. Claim 100 is objected to due to the recitation of "wherein the polypeptide at least 70% sequence identity to SEQ ID NO: 2". For clarity, it is suggested that the term be amended to recite "wherein the polypeptide has at least 70% sequence identity to SEQ ID NO: 2". Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 42-55 and 93-106 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claims 42, 93, 100 and 106 (claims 43-55, 94-99, 101-105 dependent thereon) are indefinite in the recitation of "(b) sequence complementary to (a)" for the following reasons. The term "complementary" renders the claim indefinite because it is unclear which "complements" are encompassed by the claims. Fragments of any size which are complementary to the polynucleotides claimed can be considered as "complements". Applicants have not define the term "complement", as it relates to size, in the specification either. If applicants wish to claim the entire complementary sequence, it is suggested that the term "complementary" be replaced with "completely complementary". For examination purposes, the suggested language will be used. Correction is required. It is noted that this rejection was applied to claims 42-55 in previous Office Action Paper No. 15, page 5, mailed on 8/12/2003.

8. Claim 106 is indefinite in the recitation of "hybridizing under stringent conditions" as it is unclear which polynucleotide is recited absent a statement of the conditions under which the hybridization reaction is performed. Nucleic acids which will hybridize under some hybridization conditions will not necessarily hybridize under different conditions. Furthermore, the specification discloses several conditions as stringent conditions. For examination purposes, the term will be interpreted as "hybridizing under any conditions". Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 42-55 remain rejected and newly added claims 93-104 and 106 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection was applied to claims 42-55 in a previous Office Action (Paper No. 15).

11. Applicants argue that the issue of "any function" has been addressed by amending the claims such that they are now directed to methods comprising generating variants of a genus of amidase encoding nucleic acids. According to Applicants only structurally and functionally related nucleic acids are encompassed by the scope of the claims. Thus, it is Applicant's contention that the instant claims satisfy the written description requirement of 35 USC 112, first paragraph. Applicants submit that there is no bright rule that a single species is not sufficient to put one of skill in the art in possession of the claimed genus. Applicants direct the Examiner's attention to Example 14 of the USPTO Guidelines

concerning compliance with the written description requirement. Applicants argue that, like in Example 14, the genus of nucleic acids used in the claimed method is described by structure, a physico-chemical property, and function. It is also Applicant's contention that the genus of nucleic acids used in the claimed method complies with the requirements set forth in University of California v. Eli Lilly & Co. Applicants further refer to additional case law and assert that the function of the amidases encoded by the nucleic acids used in the claimed method is sufficiently correlated to a particular known structure and a physical property (% sequence identity or specific hybridization conditions). Applicants refer to several US patents submitted in Exhibit B to indicate that the USPTO has issued claims directed to genera of polynucleotides based on sequence identity and stringent hybridization.

12. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection of claims 42-55 or to avoid the rejection of claims 93-104, 106. The Examiner acknowledges the amendments to the claims filed, the case law presented and Example 14 of the guidelines. However, the Examiner disagrees with Applicant's contention that the issue of "any function" has been addressed or that the instant claims are adequately described for the following reasons. The functional limitation, i.e. amidase activity, recited in claims 42 and 100 while limiting the genus of nucleic acids used in the method, encompasses a very diverse group of enzymatic activities. Amidases belong to a family of enzymes which have diverse substrates and biological functions. The specification does not teach other amidase activities but that of the polypeptide of SEQ ID NO: 2. There is no teaching in the specification which describes the critical structural elements in the polynucleotide of SEQ ID NO: 1 which are associated with every amidase activity, as recited. Furthermore, the functional limitation recited in claims 93 and 106 does not refer to the nucleic acid used in the method but rather to (1) the polynucleotide having at least 70% sequence identity to SEQ ID NO: 1, or (2) the nucleic acid having a sequence as set forth in SEQ ID NO: 1. As such, claims 93-99 and 106 are directed to a method of

generating a variant nucleic acid using nucleic acids of any function. Thus, one cannot reasonably conclude that the genus of nucleic acids required in the claimed method is adequately described .

Since the claims are directed to a method of use of (1) nucleic acids encoding polypeptides having a large variety of amidase activities, and (2) nucleic acids encoding polypeptides of any function, Applicant's arguments regarding the analogy between the written description analysis presented in Example 14 and the genus of nucleic acids used in the claimed method are found unpersuasive. Similarly, Applicant's assertion that the genus of nucleic acids required to practice the claimed method is adequately described according to the findings in *University of California v. Eli Lilly & Co.* is not persuasive as the genus of nucleic acids used in the claimed method either (1) encode polypeptides having diverse amidase activity, or (2) encode polypeptides of any function. It is also noted that even if the claims were amended to recite a specific amidase activity in regard to the nucleic acids used in the claimed method, the structural limitations recited in claims 93 and 106, i.e. (1) 30-150 consecutive nucleotides of a polynucleotide having at least 70% sequence identity to the polynucleotide of SEQ ID NO: 1, and (2) polynucleotide capable of hybridizing under any conditions to the nucleic acid of SEQ ID NO: 1, do not constitute a substantial portion of the genus as the remainder of any nucleic acid comprising said structural elements is completely undefined and the specification does not define the remaining structural features for members of the genus to be selected. Many functionally and structurally unrelated polynucleotides are encompassed by these claims. While the Examiner acknowledges that there is no rule which states that a single species is not sufficient to adequately describe a genus, as discussed in the written description guidelines, the written description requirement may be satisfied through sufficient description of a representative number of species by disclosure of relevant identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. When there is

substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus. Thus, one of skill in the art cannot reasonably conclude that the genus of nucleic acids required to practice the claimed method is adequately described by a single species.

In regard to Exhibit B, while the Examiner acknowledges the many patents presented, it is noted that each patent application is examined on its own merits according to the current guidelines of examination as set forth by the USPTO and a discussion on the written description of the claimed inventions in those patents would require a detailed review of the record of each individual case, which would be improper herein.

13. Claims 42-55, 93-104, and 106 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of generating a variant nucleic acid using the nucleic acid of SEQ ID NO: 1 or a nucleic acid encoding the polypeptide of SEQ ID NO: 2, does not reasonably provide enablement for a method of generating a variant nucleic acid using (1) a nucleic acid comprising a polynucleotide having at least 70%-95% sequence identity to the polynucleotide of SEQ ID NO: 1, wherein the polynucleotide encodes any amidase, (2) a nucleic acid comprising a polynucleotide encoding any amidase which has at least 70% sequence identity to the polypeptide of SEQ ID NO: 2, (3) a nucleic acid encoding a polypeptide of any function wherein the nucleic acid hybridizes under any conditions to the polynucleotide of SEQ ID NO: 1, or (4) a nucleic acid encoding a polypeptide of any function, wherein the nucleic acid comprises at least 30-150 consecutive nucleotides of a polynucleotide encoding any amidase, and wherein the polynucleotide has at least 70% sequence identity to the polynucleotide of SEQ ID NO: 1. The specification does not enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. This rejection was applied to claims 42-55 in a previous Office Action (Paper No. 15).

14. Applicants argue that the specification enabled the skilled artisan at the time of the invention to identify, make and use a genus of amidases to practice claimed the invention. Applicants refer to a declaration by inventor Jay Short, who declares that the state of the art at the time of the invention and the level of skill of the person of ordinary skill in the art was very high. Dr Short's declaration further states that one of skill in the art at the time of the invention could use the teachings of the specification and other protocols known in the art to screen for nucleic acids encoding polypeptides having amidase activity and that while the number of samples needed to be screened may have been high, the screening procedures were routine and successful results predictable. According to Dr. Short's declaration, knowledge of the specific structural elements which correlate with amidase activity would not have been required to create variants and test them for activity. Applicants further argue that enablement is not precluded by the necessity to screen large number of compositions as long as that screening is routine. Applicants refer to *Hybritech, Inc. v. Monoclonal Antibodies, Inc.* as support for the argument that the claimed invention is enabled even if there is a need to screen numbers of negatives to find a sample with the desired activity.

15. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection of claims 42-55 or to avoid the rejection of claims 93-104, 106. As indicated above, the claims are still drawn to either (1) a method of use of a genus of nucleic acids encoding polypeptides of any function, or (2) a method of use of a genus of nucleic acids encoding any amidase. See scope of the claims described above. The scope of the claims is not commensurate with the enablement provided in view of the extremely large number of polynucleotides encoding polypeptides of <u>any function,</u> or encoding <u>any</u> amidase encompassed by the claims as well as the lack of knowledge in regard to the

correlation between any amidase activity and structure, such that one of skill in the art would reasonably conclude that the disclosure is enabling for the full scope of the claims.

As indicated in the previous Office Action (Paper No. 15) and reiterated herein, the specification is completely silent in regard to which are the critical structural elements in a polynucleotide to encode a polypeptide having any amidase activity nor does it teach which amino acid residues can be substituted, deleted, or inserted in the polypeptide of SEQ ID NO: 2 to obtain structural homologs of the polypeptide of SEQ ID NO: 2 as recited in the claims which retain any amidase activity. The art, as evidenced by Bork, Broun et al., Van de Loo et al., Witkowski et al. and Seffernick et al., clearly teaches the unpredictability of assigning function based on structural homology and how small structural changes can lead to major changes in function. Therefore, in the absence of any information as to how structure correlates with function, one of skill in the art would have to go through the burden of undue experimentation to isolate/make the polynucleotides, as encompassed by the claims, to practice the full scope of the claimed method.

The Examiner acknowledges the ruling in *Hybritech, Inc. v. Monoclonal Antibodies, Inc* as well as the declaration by inventor Jay Short, and agrees that enablement is not precluded by the need of screening a number of compositions as long as the screening is routine. Furthermore, the Examiner agrees that creation of variants having the structural limitations recited in the claims is routine in the art. However, the Examiner disagrees with Applicant's contention that testing the extremely large number of variants encompassed by the claims is not undue experimentation when there is no guidance or knowledge as to which are the structural elements in the polypeptide of SEQ ID NO: 2 that correlate with any amidase activity. It is not routine in the art to randomly create an infinite number of variants and test them for activity. Instead, as indicated above, one of skill in the art would have some knowledge or guidance as to how structure correlates with function such that a reasonable number of variants with the potentiality of having the desired function can be created and tested. Thus, in view of the information

provided, the lack of relevant examples, the lack of knowledge about the critical structural elements required for any amidase activity, and the unpredictability of the art in regard to accurate annotation of function based on structural homology, one of skill in the art cannot reasonably conclude that the specification is enabling for the full scope of the claimed invention.

Conclusion

16. No claim is in condition for allowance.

17. Applicant's amendment of claims 42-55 and addition of claims 93-106 necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

18. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 872-9306. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

19. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (571) 272-0928. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1234.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
May 3, 2004

REBECCA E. PRUTY
PRIMARY EXAMINER
GROUP ~~1600~~ 1640